Guidance for Industry
Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing

DRAFT GUIDANCE

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For questions regarding this draft document contact the CDER, Office of Clinical Pharmacology's Guidance and Policy Team at CDER_OCP_GPT@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Revision 2

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4

5
6 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
7 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
8 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
9 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
10 for this guidance as listed on the title page.
11

12
13
14
15 **I.   INTRODUCTION**
16
17 This guidance assists sponsors in the design and analysis of studies[2] that assess the influence of
18 impaired renal function on the pharmacokinetics (PK) and/or pharmacodynamics (PD) of an
19 investigational drug and addresses how such information can inform the labeling. This version[3]
20 revises and replaces the draft guidance entitled *Pharmacokinetics in Patients With Impaired*
21 *Renal Function — Study Design, Data Analysis and Impact on Dosing and Labeling* (March
22 2010) and provides updated recommendations on the following topics:
23
24 • When a standalone study of a drug's PK in subjects with impaired renal function is
25   recommended and when it may not be needed
26
27 • The design and conduct of pharmacokinetic studies in subjects with impaired renal
28   function
29
30 • Considerations for characterizing a drug's PK in patients undergoing intermittent or
31   continuous dialytic therapies
32

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[1] This guidance has been prepared by the Renal Impairment Guidance Working Group in the Center for Drug
Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

[2] For the purposes of this guidance, studies and trials are used interchangeably.

[3] The updates in this guidance are in part based on the discussion at an FDA Advisory Committee Meeting in May
2019: https://www.fda.gov/advisory-committees/advisory-committee-calendar/may-7-2019-meeting-
pharmaceutical-science-and-clinical-pharmacology-advisory-committee-meeting#event-materials.

33   • The use of pharmacokinetic information from phase 2 and 3 studies to inform dosing
34   recommendations for patients with impaired renal function
35
36   • The analysis and reporting of the results of studies that characterize the impact of
37   impaired renal function and how these data inform dosing recommendations in labeling
38
39   FDA's guidance documents, including this guidance, do not establish legally enforceable
40   responsibilities. Instead, guidances describe the Agency's current thinking on a topic and are to
41   be viewed only as recommendations, unless specific regulatory or statutory requirements are
42   cited. The use of the word *should* in Agency guidances means that something is suggested or
43   recommended, but not required.
44
45
46   **II.   BACKGROUND**
47
48   Drugs are eliminated from the body by a variety of mechanisms. Most drugs are cleared by a
49   combination of some or all of the following pathways: metabolism and transport in the small
50   intestine, metabolism and transport in the liver, and glomerular filtration and tubular secretion of
51   unchanged drug by the kidneys (i.e., renal excretion). If a drug is eliminated primarily through
52   renal excretion, then impaired renal function usually alters the drug's PK to an extent that a
53   change in the dosage regimen from that used in patients with normal renal function should be
54   considered.
55
56   The most obvious type of change in the PK of a drug arising from impaired renal function is a
57   decrease in renal excretion of the drug or its metabolites. However, impaired renal function has
58   also been associated with changes in the absorption, plasma protein binding, and/or tissue
59   distribution of a drug. Literature reports indicate that impaired renal function can alter some
60   drug metabolism and transport pathways in the liver and gut.[4,5] These changes can be
61   particularly prominent in patients with severely impaired renal function. These topics are an area
62   of active research, and the findings from this research could inform FDA guidance in the future.
63
64   As a result of the above considerations, for most drugs that are likely to be administered to
65   patients with impaired renal function, it is important to characterize a drug's PK in subjects with
66   impaired renal function to provide appropriate dosing recommendations. Exceptions to this
67   recommendation are described in section I.C.
68

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[4] Sun, H, L Frassetto, and LZ Benet, 2006, Effects of Renal Failure on Drug Transport and Metabolism, Pharmacol Ther, 109:1–11.

[5] Nolin, TD, J Naud, FA Leblond, and V Pichette, 2008, Emerging Evidence of the Impact of Kidney Disease on Drug Metabolism and Transport, Clin Pharmacol Ther, 83:898–903.

69
70 **III.   CONSIDERATIONS FOR RENAL IMPAIRMENT STUDIES**
71
72 The safety and effectiveness of a drug are generally established for specific dosage regimens in
73 late-phase clinical trials that enroll patients from the target patient population. Frequently,
74 individuals with advanced renal disease are explicitly excluded from participation in these trials.
75 Drug development programs should include an early characterization of the expected effect of
76 impaired renal function on a drug's PK, with the goal of enabling the inclusion of this population
77 in late-phase trials by allowing appropriate prospective dosage adjustment.
78
79 Early characterization can be based on data obtained from phase 1 and/or phase 2 studies.
80 Alternatively, this information can be obtained by utilizing modeling and simulation strategies,
81 for example, physiologically based pharmacokinetic modeling and simulation. Such approaches
82 allow sponsors to obtain clinical experience using the proposed dosing regimen in patients with
83 impaired renal function and thus better ensure that the trial findings will be applicable to the
84 population likely to use the drug, should it be approved. [6,7]
85
86 Alternative enrollment designs, such as sequential or adaptive enrollment of patients with
87 progressively worsening categories of renal function can also be considered to support the safe
88 enrollment of patients. The exclusion of patients with impaired renal function from clinical
89 studies conducted for a development program should be justified and discussed with the relevant
90 review divisions.
91
92   **A.   Circumstances Where a Dedicated Study Is Recommended**
93
94   *1.   Drugs Excreted Primarily Via Renal Mechanisms*
95
96 A dedicated renal impairment study is generally recommended: (1) when the drug is likely to be
97 used in such patients; and (2) when impaired renal function is likely to alter the PK of the drug or
98 its active metabolites because they are substantially eliminated by the renal route. A drug is
99 considered to be substantially eliminated by the renal route when the fraction of systemically
100 available drug or active metabolite that is eliminated unchanged in the urine (f_e) is 0.3 or greater.
101

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[6] See the FDA draft guidance entitled *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (June 2019). When final, this guidance will represent the FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[7] See the FDA final guidance entitled *Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies Guidance for Industry* (July 2020).

| 102 | | 2. | *Certain Biologic Drugs (Therapeutic Proteins and Peptides)* |

103
104   Data from biologics license application reviews indicate that impaired renal function decreased
105 the renal clearance of therapeutic proteins and peptides that have a molecular weight of less than
106 69 kDa. In some cases, a dose adjustment was necessary to reduce the risk of exposure-related
107 toxicity in patients with impaired renal function. Therefore, pharmacokinetic studies in patients
108 with impaired renal function are recommended for therapeutic proteins and peptides with a
109 molecular weight less than 69 kDa.
110
111   *3.*   *Evaluating the Influence of Dialytic Therapies*
112
113   The PK of drugs that are likely to be used in patients with end-stage renal disease (ESRD)
114 undergoing dialysis should be evaluated both while the patient is on dialysis and off dialysis to
115 determine the contribution of the dialytic method to the elimination of the drug and its
116 potentially active metabolites (see section I.E). Dialytic therapies can remove a significant
117 fraction of a drug or its active metabolites, leading to clinically significant exposure changes. In
118 such cases, a change in the dosage regimen, such as a supplemental dose following the dialysis
119 procedure, could be appropriate.
120
121   Intermittent hemodialysis (IHD) is the most common dialytic modality used in patients with
122 ESRD in the United States. Therefore, to evaluate the impact of dialysis on the PK of a drug, we
123 recommend that sponsors conduct these studies in patients undergoing IHD. When relevant to
124 the intended patient population, similar principles can be applied to characterize the impact of
125 peritoneal dialysis or continuous renal replacement therapy (CRRT) on the disposition of the
126 drug and/or its metabolites.
127
128   A study of the effect of dialytic therapies on the PK of a drug can be omitted if the dialytic
129 procedure is unlikely to result in significant elimination of the drug or its active metabolites, for
130 example, if the drug:
131
132   •   Has a molecular weight that makes it unlikely to be cleared by dialytic modalities
133   •   Exhibits high plasma protein binding that is not affected by impaired renal function
134
135   **B.   Circumstances Where a Dedicated Study Can Be Considered**
136
137   As mentioned in section II, it is often important to characterize the impact of impaired renal
138 function on the PK of drugs that are eliminated predominantly via nonrenal routes. In such
139 situations, a reduced pharmacokinetic study design (described in section I.C) can be considered.
140
141   **C.   Circumstances Where a Dedicated Study May Not Be Important**
142

143 For some drugs, impaired renal function is not likely to alter the PK of a drug enough to justify
144 dosage adjustment. In such cases, a dedicated study is generally not necessary. Current
145 knowledge suggests that the following drug properties justify this approach:
146
147 • Gaseous or volatile drugs and active metabolites that are primarily eliminated through the
148 lungs
149
150 • Drugs intended only for single-dose administration
151
152 • Therapeutic proteins with a molecular weight greater than 69 kDa
153
154 • Locally acting drugs (e.g., topical products) with limited systemic absorption
155
156
157 **IV.   STUDY DESIGN**
158
159 The primary goal is to characterize the impact of impaired renal function on the PK of the drug
160 and determine whether the extent of the changes in the PK of the drug warrant a dose adjustment.
161 Achieving this goal can be accomplished in a variety of ways, depending on the characteristics of
162 the drug and the intended patient population. This section discusses:
163
164 • Determination of renal function in adults
165
166 • Design of a full pharmacokinetic study
167
168 • Design of a reduced pharmacokinetic study
169
170 • Evaluation of the impact of impaired renal function on the PK of a drug in phase 2 or
171 phase 3 studies
172
173 • Design of studies in patients receiving dialytic therapies
174
175 • Considerations for pharmacodynamic or other response assessments
176
177   **A.   Determination of Renal Function**
178
179 There are different ways to assess renal function. Measurement of the glomerular filtration rate
180 (GFR) using exogenous markers such as inulin, iothalamate, EDTA, diethylene triamine
181 pentaacetic acid, and iohexol provides a more accurate assessment of renal function than
182 estimating equations. In addition, measured creatinine clearance (CLcr) using timed urine
183 samples is sometimes used to assess renal function. However, these methods are not routinely

184 used in clinical practice and estimation of renal function using a widely accepted serum
185 creatinine-based equation is usually sufficient for pharmacokinetic studies.
186
187 Serum creatinine-based equations include:
188
189   (1) Estimated GFR (eGFR) calculated using a contemporary, widely accepted equation
190   for the population being studied.[8,9] In clinical practice, eGFR values are standardized to
191   a body surface area (BSA) value of 1.73 m^2 and expressed and reported in units of
192   mL/min/1.73 m^2. Renal clearance of a drug is proportional to individual GFR (expressed
193   as mL/min) and not BSA-standardized GFR, hence BSA-standardization will not be
194   appropriate in patients with BSAs different than the standard (1.73 m^2). To individualize
195   GFR for drug dosing, multiply the standardized GFR by the individual's BSA calculated
196   using an appropriate formula[10,11] and divide by 1.73.
197
198   (2) Estimated creatinine clearance (CLcr) in mL/min calculated using the Cockcroft-
199   Gault (C-G) equation.[12] In overweight or obese individuals, use of alternative body
200   weight metrics such as ideal body weight (IBW) or adjusted body weight (ABW) when
201   calculating CLcr is likely to provide a more accurate estimate of renal function than total
202   body weight.[13]
203

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[8] Levey AS, LA Stevens, CH Schmid, YL Zhang, AF Castro 3rd, Feldman HI, JW Kusek, P Eggers, F Van Lente, T Greene, J Coresh, CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), 2009, A New Equation to Estimate Glomerular Filtration Rate, Ann Intern Med, 150(9):604-12.

[9] Levey AS, J Coresh, T Greene, LA Stevens, YL Zhang, S Hendriksen, JW Kusek, F Van Lente, Chronic Kidney Disease Epidemiology Collaboration, 2006, Using Standardized Serum Creatinine Values in the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate, Ann Intern Med, 145(4):247-54.

[10] Dubois D, EF Dubois, 1916, A Formula to Estimate the Approximate Surface Area if Height and Weight Be Known, Arch Intern Med, 17:863-871.

[11] Mosteller RD, 1987, Simplified Calculation of Body Surface Area, N Engl J Med, 317:1098.

[12] Cockcroft, DW and MH Gault, 1976, Prediction of Creatinine Clearance from Serum Creatinine, Nephron, 16(1):31-41.

[13] Pai, MP, 2010, Estimating the Glomerular Filtration Rate in Obese Adult Patients for Drug Dosing, Advances in Chronic Kidney Disease, 17(5):e53-e62.

204   Because of the widespread availability and incorporation of eGFR into current clinical practice,
205   use of eGFR to determine renal function in pharmacokinetic studies is recommended.[14, 15]
206   However, given the strengths and limitations of each method, use of measured GFR (using an
207   exogenous marker), measured CLcr, or any contemporary, widely accepted, and clinically
208   applicable estimating equation for the population being studied is considered reasonable to assess
209   renal function in PK studies.
210
211   In pediatric patients, renal function can also be either measured or estimated. There are
212   multiple equations for estimation, and, as with adults, any widely accepted contemporary
213   equation for use in pediatric patients is acceptable. In pediatric patients below two years of
214   age, maturation, gestational age and other factors need to be taken into account. Therefore,
215   early communication with the Agency is recommended. For our draft recommendations on
216   assessing renal function in pediatric patients, refer to the FDA draft guidance for industry
217   entitled *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and*
218   *Biological Products* (December 2014).[16]
219
220   **B.   Full Pharmacokinetic Study Design**
221
222   A full PK study design is recommended for drugs that are described in Section III.A.
223
224   *1.   Study Participants*
225
226   To adequately characterize the impact of impaired renal function on the PK of a drug, the renal
227   function of study participants should range from normal function to severe impairment. The
228   classification of renal function described in Table 1 can be used to enroll participants into the
229   dedicated renal impairment study. It can also help derive dosing recommendations.
230
231
232
233
234
235

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[14] Hudson, JQ and TD Nolin, 2018, Pragmatic Use of Kidney Function Estimates for Drug Dosing: The Tide is Turning, Advances in Chronic Kidney Disease, 25(1):14-20.

[15] Matzke, GR, GR Aronoff, AJ Atkinson Jr, WM Bennett, BS Decker, KU Eckardt, T Golper, DW Grabe, B Kasiske, F Keller, JT Kielstein, R Mehta, BA Mueller, DA Pasko, F Schaefer, DA Sica, LA Inker, JG Umans, P Murray, 2011, Drug Dosing Consideration in Patients With Acute and Chronic Kidney Disease: A Clinical Update From Kidney Disease: Improving Global Outcomes (KDIGO), Kidney International, 80(11):1122-1127.

[16] When final, this guidance will represent the FDA's current thinking on this topic.

236 **Table 1. Classifications of Renal Function[a,b] for Dedicated Renal Impairment Studies**

Description	Range of Values for Renal Function (mL/min)
Control (normal renal function)	≥ 90
Mild impairment	60-89
Moderate impairment	30-59
Severe impairment	15-29
Kidney failure[c]	<15 or dialysis patients on non-dialysis days

237
238 [a] eGFR: estimate of GFR based on an estimation equation and expressed in mL/min. To convert mL/min/1.73 m^2 to
239 mL/min multiply by the individual's BSA calculated using an appropriate formula and divide by 1.73.
240
241 [b] CLcr: estimated creatinine clearance based on the C-G equation.
242
243 [c] Kidney failure: This classification is strictly for the purposes of conducting a dedicated renal impairment study and
244 should not be used for the purposes of classifying kidney disease.
245

246 To characterize the impact of impaired renal function on the PK of drugs that are expected to
247 have a wide therapeutic range, study subjects can be stratified based on renal function $\geq$60
248 mL/min (normal renal function or mild renal impairment), 15-59 mL/min (moderate to severe
249 renal impairment), and <15 mL/min or dialysis patients on non-dialysis days.
250

251 Subjects with impaired renal function should be hemodynamically stable. Further, subjects with
252 impaired renal function should be similar to the reference group with respect to factors known to
253 affect the drug's PK. Subjects taking medications that are likely to impact drug metabolism or
254 excretion should be excluded from renal impairment studies.
255

256 Ideally, the control group in this study should be representative of the typical patient population
257 for the drug under study, considering the patients' renal function and other factors known to
258 affect the drug's PK.
259

260   2.   *Sample Size*
261

262 The number of subjects enrolled in each renal function group should be sufficient to ensure
263 precise estimation of the relevant pharmacokinetic parameters. Justification should be provided
264 for the sample size selected. For example, one approach could be to prospectively target a 95
265 percent confidence interval within 60 percent and 140 percent of the geometric mean estimate of
266 relevant pharmacokinetic parameters for the drug in each renal function group with at least 80

267   percent power.[17]

268

269   *3.   Drug Administration*

270

271   A single-dose study is usually sufficient to accurately describe the PK of the drug and its active
272   metabolites, especially when the drug and active metabolites exhibit dose-proportional and time-
273   independent PK at the concentrations anticipated in the patients to be studied. In rare cases, e.g.
274   when the drug shows dose- or time-dependent PK, a multiple-dose study should be conducted.

275

276   In most single-dose studies, the same dose can be administered to all patients regardless of renal
277   function, because the peak concentration of a drug is not substantially affected by renal function.
278   In multiple-dose studies, lower doses or less frequent administration can be considered in
279   patients with impaired renal function to prevent the accumulation of the drug and its metabolites.
280   The dosage regimen can be adjusted based on the best available pre-study estimates of the PK of
281   the drug and its active metabolites in patients with impaired renal function. In multiple-dose
282   studies, the dosing should be continued long enough to achieve steady-state drug levels. A
283   loading dose strategy can be considered to shorten the time to reach steady-state drug levels,
284   particularly if the elimination half-life is greatly prolonged in patients with impaired renal
285   function.

286

287   *4.   Sample Collection and Analysis*

288

289   Plasma or whole blood as well as urine samples should be collected and analyzed for the parent
290   drug and any metabolites of interest. The frequency and duration of plasma sampling and urine
291   collection should be sufficient to accurately estimate the relevant pharmacokinetic parameters for
292   the parent drug and its active metabolites (see section V).

293

294   Plasma protein binding is often altered in patients with impaired renal function. For systemically
295   active drugs and metabolites, the unbound concentrations generally determine the rate and extent
296   of delivery to the sites of action. Measurement of unbound drug concentrations is recommended
297   for each plasma sample only if the binding is concentration-dependent or is affected by
298   metabolites or other time-varying factors. Otherwise, the unbound fraction should be determined
299   using a limited number of samples or even a single sample from each patient. For drugs and
300   metabolites with a low extent of plasma protein binding (e.g., less than 80 percent), changes in
301   PK resulting from alterations in protein binding due to impaired renal function are generally
302   expected to be small relative to those in patients with normal renal function. In such cases, a
303   description and analysis of the PK of the drug or metabolite in terms of total concentrations is
304   sufficient.

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[17] Wang Y, PR Jadhav, M Lala, J Gobburu, 2012, Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies, J Clin Pharmacol, 52(10):1601-1606.

305
306   **C.**   **Reduced Pharmacokinetic Study Design**
307
308 For drugs that are predominantly eliminated via nonrenal routes and likely to be used in patients
309 with impaired renal function, a reduced study design can be used to determine the need for dose
310 adjustment. The intent of a reduced study design is to represent a *worst-case* scenario, i.e., one
311 that shows the greatest impact impaired renal function could have on the PK of the drug. Prior
312 submissions to the Agency and literature reports suggest that for such a study, subjects with
313 severe renal impairment (see Table 1) can be considered to represent the worst-case scenario.[18]
314 If a reduced pharmacokinetic study shows a clinically relevant effect on the PK of the drug in
315 subjects with severe renal impairment, the sponsor should characterize the effect of impaired
316 renal function on the drug's PK in subjects with the remaining levels of impaired renal function
317 (see Table 1). If no difference in PK is observed between patients at the extremes of renal
318 function, then no further study is recommended. Other study design considerations described in
319 sections IV.B also apply to this setting.
320
321   **D.**   **Characterizing the Impact of Renal Function in Phase 2 and Phase 3 Trials**
322
323 If there is adequate representation of patients with varying degrees of renal function (see section
324 III), as well as sufficient data to describe the impact of impaired renal function on the PK of the
325 drug, population pharmacokinetic (popPK) analyses of data from phase 2 and/or phase 3 clinical
326 trials could be sufficient to characterize the impact of renal function on drug exposure for the
327 population that was represented in the trials. If patients with severe renal impairment were not
328 enrolled in sufficient numbers, a reduced design renal impairment study could be needed to
329 provide appropriate dosing recommendations in labeling for the impaired renal function
330 population not represented in clinical trials. When possible, renal function should be assessed as
331 independent predictor of exposure-response relationships.
332
333 To allow for successful use of a popPK approach or exposure-response analysis, the study design
334 should retain some of the critical components of the dedicated renal impairment studies
335 described in the previous section on full study designs (section IV.B). The following are
336 important considerations:
337
338   •   Sufficient numbers of patients over a range of renal function
339
340   •   Accurate records of dosing and sample collection times
341

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[18] Zhang L, Xu N, Xiao S, Arya V, Zhao P, , Lesko LJ, Huang SM, 2012, Regulatory Perspectives on Designing Pharmacokinetic Studies and Optimizing Labeling Recommendations for Patients with Chronic Kidney Disease, J Clin Pharmacol, 52(1 Suppl): 70S-90S.

342   • Adequate numbers of samples per patient
343
344   • Unbound drug concentrations when appropriate
345
346   • Active metabolite levels, where applicable, in addition to levels of the parent drug
347
348   • Use of the same measure of estimated renal function, especially when data are pooled
349   across studies
350
351   • Exposure-response analyses, when available, should account for impaired renal function
352   as an independent predictor of response
353
354 For additional information on the application of popPK approaches, refer to the FDA draft
355 guidance for industry entitled *Population Pharmacokinetics* (July 2019).[19]
356
357   **E.   Effect of Dialytic Therapies on the PK of a Drug**
358
359 The primary questions to be addressed by studying the effect of dialytic therapies on the PK of a
360 drug are: (1) whether the drug dosage should be adjusted because of dialysis; (2) if so, by how
361 much; (3) and the timing of drug administration relative to dialysis. The results of the study also
362 provide insight regarding the value of dialysis for the treatment of a drug overdose.
363
364   *1.   Intermittent Dialytic Therapies*
365
366 This section mainly focuses on intermittent hemodialysis (IHD) as it is the most common
367 dialysis method used in ESRD patients in the United States. However, some of the general study
368 design principles described below for IHD can be applied to other modalities.
369
370 It is critical for the IHD study to include both on- and off-dialysis periods. Each subject can
371 receive a single dose on two occasions, once with the dose administered prior to a dialysis
372 session, with dialysis typically commencing just before the anticipated T_{max} following
373 administration of the drug. On the second occasion, the drug should be administered in such a
374 way that it reflects the exposures expected during an off-dialysis day (e.g., not in close proximity
375 to the end of a dialysis session).
376
377 Because most dialysis centers in the United States currently use high-flux dialyzers during IHD,
378 pharmacokinetic studies should be conducted in patients being treated with high-flux IHD. It is
379 important to record the blood flow (Q_B), dialysate flow (Q_D), and the make and model of the
380 dialyzer used in the study to interpret study results and extrapolate to other dialysis conditions.

---

[19] When final, this guidance will represent the FDA's current thinking on this topic.

381
382   2.   *Continuous Dialytic Therapies*
383
384   For critical care medications likely to be used in patients on continuous renal replacement
385   therapy (CRRT), the findings from IHD studies might not be sufficient to derive dosing
386   recommendations for patients using this modality. Therefore, it is important to evaluate the
387   impact of CRRT on the PK of the drug to derive appropriate dosing recommendations. Given
388   the practical challenges (e.g. the patient's hemodynamic stability and the difficulty in obtaining
389   blood samples) when conducting such a study, planning optimal sampling times is critical for the
390   collection of relevant pharmacokinetic information in this setting. In addition, the methods for
391   CRRT vary widely across institutions. As far as it is practicable, it is important to design and
392   conduct these studies so that the results are generalizable across CRRT settings. A single-dose
393   study is acceptable and can be the most feasible approach. If a multiple-dose assessment is
394   possible, it can characterize the effect of CRRT as a patient's condition changes. One approach
395   that could allow collection of information that informs dosage is to use a fixed blood flow rate
396   (Q_B) with one or two commonly prescribed effluent flow rates (Q_E).[20] Sponsors are strongly
397   encouraged to seek FDA's input early in the process of designing such studies.
398
399   3.   *Sample Collection and Data Analysis*
400
401   To accurately estimate the clearance in ESRD patients undergoing IHD during the non-dialysis
402   (or between dialysis) period, dosing and sampling times should be planned to capture the full
403   pharmacokinetic profile of the drug and, where applicable, its active metabolites.
404
405   To determine the clearance during dialysis, blood samples should be collected pre-dialysis and at
406   appropriate intervals during the dialysis period. The entire dialysate should be collected, its
407   volume recorded, and a sample retained to determine drug concentrations.
408
409   Concentrations of the drug and any active metabolites should be measured in the blood entering
410   the dialyzer as well as dialysate samples. The total amount of drug removed in the dialysate
411   should be determined. The dialysis clearance (CL_D) can be calculated from the equation below,
412   where t_0 marks the start time, and t_1 is the time of termination of the hemodialysis session:
413
414
$$CL_D = \frac{Amount\ Recovered}{AUC_{t_0-t_1}}$$

415

---

[20] Nolin TD, GR Aronoff, WH Fissell, L Jain, R Madabushi, K Reynolds, L Zhang, SM Huang, R Mehrotra, MF Flessner, JK Leypoldt, JW Witcher, I Zineh, P Archdeacon, P Roy-Chaudhury, SL Goldstein, 2015, Pharmacokinetics Assessment in Patients Receiving Continuous RRT: Perspectives from Kidney Health Initiative, Clin J Am Soc Nephrol, 10(1):159–164.

416 Blood samples before and at the end of dialysis should also be used to measure drug binding to
417 plasma proteins. The fraction of the administered dose that is recovered in the dialysate should
418 be calculated to assess the need for administering supplemental drug doses to hemodialysis
419 patients.
420
421 The analysis should also consider the potential for a rebound due to redistribution of drug from
422 peripheral tissues after dialysis and characterize its implications for drug dosing.
423
424   **F.**   **Considerations for Pharmacodynamic Assessments**
425
426 Whenever appropriate and feasible, pharmacodynamic assessments should be included in studies
427 of impaired renal function. Such assessments will be important in situations where changes in
428 renal function result in pharmacodynamic changes that are independent of pharmacokinetic
429 changes (e.g., oral anticoagulants). In such situations, the pharmacokinetic and
430 pharmacodynamic data could be critical to derive appropriate dosage adjustments for patients
431 with impaired renal function. The selection of the pharmacodynamic endpoints should be
432 discussed with the appropriate FDA review staff.
433
434
435 **V.**   **DATA ANALYSIS**
436
437   **A.**   **Estimating Pharmacokinetic Parameters**
438
439 Plasma concentration data and urinary excretion data should be analyzed to estimate PK
440 parameters of the drug and its active metabolites. The pharmacokinetic parameters of interest
441 include the area under the plasma concentration-time curve (AUC), peak concentration (C_{max}),
442 fraction unbound (f_u), apparent clearance (CL/F), renal clearance (CL_R), apparent nonrenal
443 clearance (CL_{NR}/F), apparent volume of distribution (V/F), and effective and terminal half-life
444 ($t_{1/2}$), where applicable. The pharmacokinetic parameters of active metabolites can include the
445 AUC, C_{max}, CL_R, and $t_{1/2}$. Non-compartmental and/or compartmental modeling approaches to
446 parameter estimation can be employed.
447
448   **B.**   **Modeling the Relationship Between Renal Function and Pharmacokinetic**
449   **Parameters**
450
451 The FDA recommends a regression approach in which estimated renal function and the
452 pharmacokinetic parameters are treated as continuous variables. This method is usually
453 preferred to an analysis in which estimated renal function is treated as a categorical variable
454 corresponding to the normal, mild, moderate, and severe renal impairment groups. In either
455 case, the potential for confounding due to differences in baseline covariates that can affect a
456 drug's PK (e.g., age, gender, race, and weight) should be evaluated.
457

458 The sponsor should calculate and report estimates of the parameters of the chosen model as well
459 as measures of their precision (e.g., standard errors or confidence intervals).
460
461 ### C.   Developing Dosage Recommendations in Patients with Renal Impairment
462
463 Dosage recommendations in patients with impaired renal function should be determined based
464 on the overall understanding of the relationship between renal function, drug exposure, and the
465 exposure-response relationships (efficacy and safety). For drugs with a wide therapeutic range,
466 changes in the drug's PK based on renal function might not always result in a dosage adjustment
467 for patients with impaired renal function. When there is a need for a different dosage
468 recommendation in patients with impaired renal function compared to those with normal renal
469 function, these dosage recommendations should be based on exposure-matching to a reference
470 group with an acceptable benefit-risk profile for the drug. The reference group does not have to
471 be limited to patients with normal renal function.[21]
472
473 There are a number of approaches to dosage selection for patients with impaired renal function.
474 For example, pharmacokinetic simulations that project systemic exposures that fall within the 5th
475 and 95th percentiles of those achieved in the reference group can be used. Another approach is to
476 establish no-effect boundaries, which represent an interval within which a change in systemic
477 exposure is deemed not significant enough to warrant clinical action (see also section V.B.1 in
478 the FDA final guidance for industry *Clinical Drug Interaction Studies — Cytochrome P450*
479 *Enzyme- and Transporter-Mediated Drug Interactions* (January 2020)).
480
481 The sponsor should use the data from modeling and simulation to determine the level of renal
482 function below which a different dosage is recommended. It is not necessary to rely on pre-
483 specified categories of impaired renal function as shown in Table 1.
484
485 In some situations, dosage recommendations in patients with impaired renal function can
486 significantly differ between different estimating equations of renal function. In such situations, it
487 is important to understand the reasons underlying the discrepant results and dosage
488 recommendations in the labeling should address which measure or estimating equation to use.
489
490
491 ## VI.   LABELING RECOMMENDATIONS
492
493 The Prescribing Information should include a summary of essential information about the effect
494 of renal function on the PK and PD (if known) of the drug to inform the safe and effective use of
495 the drug in patients with impaired renal function by the health care provider:

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[21] This topic was discussed at an Advisory Committee Meeting convened on May 7, 2019. Please see Footnote **Error! B ookmark not defined.** for further information.

496
497 • Renal elimination of the drug and relevant metabolites
498
499 • Pharmacokinetic or pharmacodynamic changes relative to renal function and
500   hemodialysis
501
502 • Clinical implications of these pharmacokinetic or pharmacodynamic changes
503
504 • Any recommended risk mitigation strategies in patients with renal impairment (e.g.,
505   different dosage recommendations, or monitoring recommendations)
506
507 For specific recommendations on how to incorporate use information in subjects with impaired
508 renal function in labeling, refer to 21 CFR 201.57 and the following FDA final guidances for
509 industry:
510
511 • *Labeling for Human Prescription Drug and Biological Products – Implementing the*
512   *PLR Content and Format Requirements* (February 2013).
513
514 • *Dosage and Administration Section of Labeling for Human Prescription Drug and*
515   *Biological Products — Content and Format* (March 2010).
516
517 • *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling*
518   *for Human Prescription Drug and Biological Products — Content and Format* (October
519   2011).
520
521 • *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological*
522   *Products — Content and Format* (January 2006).
523
524 • *Clinical Pharmacology Section of Labeling for Human Prescription Drug and*
525   *Biological Products — Content and Format* (December 2016)
526